

Toward Stratified Treatments for Bipolar Disorders

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Abstract

In bipolar disorders, there are unclear diagnostic boundaries with unipolar depression and schizophrenia, inconsistency of treatment guidelines, relatively long trial-and-error phases of treatment optimization, and increasing use of complex combination therapies lacking empirical evidence. These suggest that the current definition of bipolar disorders based on clinical symptoms reflects a clinically and etiologically heterogeneous entity. Stratification of treatments for bipolar disorders based on biomarkers and improved clinical markers are greatly needed to increase the efficacy of currently available treatments and improve the chances of developing novel therapeutic approaches. This review provides a theoretical framework to identify biomarkers and summarizes the most promising markers for stratification regarding beneficial and adverse treatment effects. State and stage specifiers, neuropsychological tests, neuroimaging, and genetic and epigenetic biomarkers will be discussed with respect to their ability to predict the response to specific pharmacological and psychosocial psychotherapies for bipolar disorders. To date, the most reliable markers are derived from psychopathology and history-taking, while no biomarker has been found that reliably predicts individual treatment responses. This review underlines both the importance of clinical diagnostic skills and the need for biological research to identify markers that will allow the targeting of treatment specifically to sub-populations of bipolar patients who are more likely to benefit from a specific treatment and less likely to develop adverse reactions.

Key words: bipolar disorder, stratified medicine, personalized medicine, precision medicine, treatment optimization

Psychiatric research goes to great lengths to develop tests that can predict specific therapeutic successes (Frey et al., 2013). Such tests allow for adjustment of therapies to pathological processes and are of clinical relevance if the estimation of therapeutic success based on conventional diagnostic methods is imprecise. More specifically, stratified medicine intends to bring into line diagnosis, therapy, and prevention with the genetic predisposition of patients. In the case of bipolar disorders, no risk genes and no genes associated with treatment success have been reliably identified. In this review, the term “stratified medicine” has been broadened to include all kinds of predictors of therapy success. At the end of the article, we focus on the potential of genetic and epigenetic markers in bipolar disorders.

Why stratifying treatments for bipolar disorders?

There is much evidence that conventional diagnosis of bipolar disorders is imprecise (Angst, 2004, 2008; Angst et al., 2010; Simpson et al., 2002; Zimmermann et al., 2009). While international treatment guidelines of frequent psychiatric disorders, such as major depression or schizophrenia, are relatively consistent, the guidelines for bipolar disorders are strikingly inconsistent and heterogeneous (Nivoli et al., 2011). This is particularly the case for bipolar depression in which considerable differences between recently published national and international treatment guidelines exist (Samalin et al., 2013). Despite the large number of clinical studies on bipolar depression, fundamental questions remain unclear. Thus, there is no consistent approach regarding whether bipolar depression should primarily be treated by a mono-therapy or combined therapy (Licht et al., 2008). Evidence-based expert opinions diverge considerably regarding the role of lithium and lamotrigine (Calabrese et al., 2008; Geddes et al., 2009). Additionally, the application of antidepressants is unclear (Pacchiarotti et al., 2013). Even quetiapine, with relatively consistent evidence of efficacy, is not recommended as a first-line treatment in all guidelines. Further evidence for the urgent need of better diagnosis are the relatively low mean response rates of antidepressant

(McElroy et al., 2010), anti-manic (Cipriani et al., 2011) and mood-stabilizing treatments in bipolar disorders; insufficient prediction of adverse drug reaction; long trial-and-error phases of treatment adjustment; and increasing use of complex combination therapies without solid evidence.

Stratification based on psychopathological characteristics

The American Psychiatric Association's third edition of the Diagnostic and Statistical Manual (DSM-III, 1980) aimed to operationalize clinical psychiatric diagnosis. This was required in order to study scientific diagnosis and markers regarding prediction of treatment success. A group of experts defined clusters of symptom patterns for courses as diagnostic criteria based on their clinical experience. In this way, defined diagnoses have been validated by epidemiological methods. Validation was mainly based on the criteria of Robins und Guze (Robins and Guze, 1970); the predictive efficiency and stability of diagnosis were evaluated by longitudinal studies and consistency of risk factors have been examined in family studies. As genetic risk factors in severe psychiatric diseases, such as schizophrenia and bipolar disorder, are of great importance, family studies became the most important method for validation of diagnostic criteria. The concept of bipolar disorder owes its success to family studies simultaneously conducted and published by Jules Angst und Carlo Perris (Angst and Perris, 1968). Those studies demonstrated an increased risk for bipolar disorder in relatives of bipolar patients, whereas the risk in relatives of patients suffering from major depression was not increased.

From a present-day perspective, subdivision of affective disorders into unipolar and bipolar subtypes has been a great success of psychiatric epidemiology because these subtypes are not only distinct with regard to etiology and clinical course, but also in terms of responding to pharmacologic treatment. In particular, the specific relapse prevention with lithium impressionably demonstrates the benefit of this diagnostic concept (Geddes et al., 2004).

In recent years, clinical research has identified psychopathologic markers in patients with bipolar disorder that contribute to the prediction of treatment success. Those findings describe an important step towards stratified treatments. Thus, a typical manic-depressive course with full inter-episode remission predicts a good efficiency of lithium. Mixed manic-depressive forms respond relatively well to second-generation antipsychotics, such as olanzapine or asenapine (Grunze and Azorin, 2014; Kruger et al., 2005). Agitation in manic episodes is associated with good efficiency of loxapine, asenapine, and aripiprazole (Brown et al., 2013; Kwentus et al., 2012; McIntyre et al., 2009). Seasonal forms are positive predictors for a response to light therapy (Golden et al., 2005), while forms with predominant depressive episodes predict a good prophylactic effect of lamotrigine (Colom et al., 2006). Since lithium has a potent anti-suicidal effect and reduces suicide risk by 80% in individuals with affective disorders (Baldessarini et al., 2006), an increased suicidal risk is an important predictor for the use of lithium-treatment, irrespective of its mood-stabilizing effect. This stratified use of lithium corresponds relatively well with the goal of stratified medicine to adjust therapies to disease processes. This is because we assume that lithium reduces the specific lethality of suicidal attempts by inhibition of aggressive impulses.

Besides the aforementioned progresses in clinical practice, serious disadvantages and fundamental questions remained unanswered despite decades of intensive research. There are substantial problems with the concept of bipolar disorder: 1) Depressive disorders become apparent as bipolar disorders only over time as patients are not treated in an optimum manner for years; 2) Past manic episodes are poorly remembered, which leads to further misdiagnosis (Angst et al., 2005a); and 3) There is substantial uncertainty about where to draw the line between unipolar and bipolar affective

disorders. Jules Angst and others have convincingly proven that—based on epidemiologic criteria, such as family history, course, and comorbidity—up to 40% of patients with major depressive disorders diagnosed based on the DSM-IV criteria suffer from subsyndromal hypomania and should therefore be classified as bipolar spectrum disorder (Angst et al., 2011; Angst et al., 2010). As listed in Table 1, various clinical characteristics have been identified to predict bipolar spectrum disorders (Angst et al., 2005b; Dudek et al., 2013; Lapalme et al., 1997).

However, there is evidence from placebo-controlled randomized clinical trials that subsyndromal manic states and manic symptoms are less relevant for the choice of therapeutic approach than previously assumed. Thus, antidepressants in bipolar spectrum disorders might be as effective as they are in unipolar depression (Perlis et al., 2011), and with antidepressant-treated manic symptoms, they may not occur more often in spectrum disorders than without treatment. In contrast, other studies have reported the presence of subthreshold manic symptoms as a predictor of poor antidepressant response in bipolar depression (Pacchiarotti et al., 2011). This controversy indicates that stratification based on the criteria of Robins and Guze may not necessarily contribute to stratification of treatment strategies (Robins and Guze, 1970). Only markers with predictive value in terms of therapeutic response have the potential to improve the therapeutic practice in a crucial way (Perlis, 2011). To this end, treatment studies with patients with bipolar II disorder and bipolar spectrum disorders are of high clinical relevance. Overall limits are set to personalize treatment based on psychopathologic characteristics because many clinical symptoms are unspecific and allow no inferences about the underlying disease processes.

Stratification based on endophenotypic markers

The concept of endophenotypes

Gottesman and Shields (Gottesman and Shields, 1973) recognized early a fundamental problem of psychiatric genetics. Psychiatric conditions, as defined in the DSM and other established diagnostic

manuals, do not represent adequate phenotypes for research since they are conceptualized as syndromes and are not related to mechanisms of illness. Furthermore, they assumed a long pathway from genes to clinical symptoms, which is difficult to reveal because of complex gene-by-gene interactions and gene-by-environment interactions over time. Despite intensive and expensive research, no risk genes for strong heritable psychiatric diseases like bipolar disorders and schizophrenia have been reliably identified. This seems to acknowledge that they were right (Sullivan et al., 2012). In theoretical articles, they suggested vanquishing this methodical weakness of psychiatric genetics through the implementation of endophenotypes.

Endophenotypes are intermediate phenotypes standing between genes and gene products on the one hand and clinical syndromes on the other hand. The concept of endophenotypes assumes that there are fewer genes and less complex gene-environment interactions involved in the variation of endophenotypes than in psychological syndromes (Glahn et al., 2014; Gottesman and Gould, 2003).

Thus, it seems useful to identify genetic factors underlying endophenotypes in the first step and associate the biological consequences of the identified gene variants with clinical symptoms afterwards. Endophenotypes can be categorized according a gradient between genes and clinical symptoms: for example, neuropsychological endophenotypes are located nearer to the symptoms whereas concentrations of neurotransmitters measured by magnetic resonance spectroscopy (MRS) lie nearer to the genetic pole of the gradient. In other words, the endophenotype approach assumes that genetic underpinnings of molecular biological measures is less complex than those of complex behaviors irrespective of the heritability of the phenotype's total genetic risk. (Hasler et al., 2006).

The validation criteria for endophenotypes involve the relationship with psychiatric disorders, heredity, independence from changing clinical symptomatology, and increased occurrence in healthy relatives (Hasler et al., 2006; Hasler et al., 2004). The later criterion ensures an association between the genetic risk factors of the endophenotype and those of illness (Hasler and Northoff, 2011).

Endophenotypes are not diagnostic markers in a traditional sense (i.e., specificity and sensitivity of a

specific psychiatric disorder are not validation criteria). In the context of stratified medicine (Schumann et al., 2014), it is to be expected that endophenotypes that are related to both risk genes and clinical symptoms can help to tailor psychiatric diagnostic, therapy, and prevention to pathological processes.

Neuropsychology

In schizophrenia, measures of general cognitive performance meet the validation criteria of endophenotypes (Snitz et al., 2006; Yeo et al., 2014). An advantage of such simple neuropsychological endophenotypes is that they can be effortlessly assessed in studies with large samples as well as in clinical daily routines.

Its disadvantage is that they exist near the symptom-pole on a symptom-genotype-gradient. In the case of bipolar disorder, there is an additional disadvantage that studies on neuropsychological deficits in bipolar patients and their healthy relatives revealed contradictory results (Bora et al., 2009). Common cognitive deficits appear to not be a risk factor of bipolar disorder. In fact, there is evidence that an above-average intelligence quotient during adolescence is a risk for the later occurrence of a bipolar disorder (MacCabe et al., 2010). Deficits in verbal learning and verbal memory meet the criteria of endophenotypes best (Balanza-Martinez et al., 2008; Hasler et al., 2006), followed by attention deficits and disturbance executive functions like *response inhibition* (Bora et al., 2009).

Loss of interests, reduced reaction upon positive events, and lack of motivation are core symptoms of bipolar depression, whereas uncontrollable excitation and increased motivation are core symptoms of mania. These symptoms point to dysregulation of the reward system, which is determinative of the regulation of motivation and drive. Relatively simple behavioral experiments, such as the *monetary incentive delay task* are proper for quantifying the disturbance of this system in affective disorders (Hasler et al., 2009; Knutson et al., 2008; Pizzagalli et al., 2009; Stoy et al., 2012).

Since such measures are dependent on current affective symptoms, they might not qualify for endophenotypes. The validity of such measures in terms of the underlying pathological processes in affective disorders can be improved by combining them with pharmacological manipulation. As dopamine plays a central role in the brain reward system, substances enhancing or inhibiting dopamine neurotransmission are often used (Hasler et al., 2006; Hasler et al., 2009). This approach is comparable with the glucose intolerance test, which is more convincing in the diagnosis of diabetes mellitus than simple measures of the fasting plasma glucose concentration. Nevertheless, the utility of such combined measures in research and practice are considerably limited by their complexity and costs.

Neuroeconomics

A new, important contribution derives from behavioral economics. The economic decision theory assumes that options of action are represented in the brain (Glimcher and Rustichini, 2004). The brain reward system assigns a value to each of these options (Schultz, 2006). The option of action with the greatest value will be selected and executed. Finally, the reward system evaluates the outcome, which determines future representation and evaluation processes. Extensions of this theory regard the influence of uncertainty, and temporal and social factors on decision making. Neuroeconomic research has convincingly proven that decision theory qualifies for investigation the neurobiology of the human motivation (Rangel et al., 2008). Since motivation disorders are a central feature of affective disorders, neuroeconomics has the potential to revolutionize psychiatric research (Hasler, 2012). Chandler and co-workers showed by means of behavioral experiments based on the theory of expected utility that persons with bipolar disorder exhibit a complex dysregulation of risk-evaluation which facilitates the alternations of depressive and manic phases (Chandler et al., 2009). Future research will show if such experiments are suitable to uncover pathological processes in affective disorders, which would be an important step toward stratified treatment.

Functional imaging

Current imaging methods allow the measuring of functional, structural, and chemical changes in patients with bipolar disorders. The considerable differences of these applied methods, commonly small samples, and rather low consistency of the findings complicate the possibility to describe precisely the pathological processes in bipolar or other disorders in terms of the dysfunctional brain region and neural networks.

The findings of functional imaging studies are particularly heterogeneous and therefore difficult to interpret with regard to applicability as endophenotypes (Keener and Phillips, 2007; Vargas et al., 2013). In addition, the use of psychological experiments, which differ from study to study, contribute to heterogeneity. A relatively well-examined paradigm in affective disorders is the measurement of neural reactions to emotional facial expressions. This paradigm has demonstrated a relatively consistent increased neural activity of subcortical, limbic brain regions (amygdala, parahippocampal formations, striatum) in combination with reduced activity of the lateral prefrontal cortex (Delvecchio et al., 2012). This pattern of findings is not specific for bipolar disorders but corresponds to the main finding of functional imaging studies of a broad spectrum of mood and anxiety disorders, including unipolar depression and anxiety disorder. Those findings will not be relevant for stratified medicine until it can be shown that they can be linked with therapy (e.g., if patients with strong increased subcortical activity respond better to a certain antidepressant treatment than persons without an increased activity). Antidepressants seem to be particularly efficacious in mood disorder patients with limbic hyperactivity (Chen et al., 2007; Mayberg et al., 1997). Additionally, deep brain stimulation seems to be particularly efficacious in patients with limbic hyperactivity that was normalized by stimulation (Mayberg et al., 2005). This is of special interest in the context of this review because Mayberg and colleagues recently found that deep brain stimulation is efficacious not

only in unipolar but also in bipolar depression without provoking manic or hypomanic symptoms (Holtzheimer et al., 2012).

Structural imaging

Structural imaging studies in bipolar disorders yielded four main findings: 1) Abnormal brain volume of the anterior cingulate and a decreased integrity of white matter are associated with the genetic risk for bipolar disorders (McDonald et al., 2004; Whalley et al., 2013); 2) During the course of bipolar disorder, the regional brain volume decreases (Lim et al., 2013); and 3) Lithium-treated bipolar patients exhibit larger brain volumes on average than those who are not treated with lithium (Hallahan et al., 2011). 4) The frequency of white matter atrophic alterations are higher in bipolar disorder patients than in age-matched controls (typically bright spots in T2-weighted MRI images, also referred to as white matter hyperintensities) (Ahn et al., 2004; Aylward et al., 1994; Beyer et al., 2009; Marlinge et al., 2014).

There is some evidence that excessive release of corticosteroids, glutamate neurotoxicity, mitochondrial dysfunction, and stress-induced decrease of neurotrophic factors lead to the decrease of gray matter (Munakata et al., 2005; Nugent et al., 2006; Snyder et al., 2011; Stork and Renshaw, 2005). These neurotrophic and neurotoxic processes, which putatively contribute to an increased relapse risk in the course of illness, have important implications in terms of stratification of treatments. It seems natural that pathological processes differ not only between persons but also between stages of illness. A recent Task Force Report of the International Society for Bipolar Disorders concluded that staging models have the potential to improve treatment selection in bipolar disorders, and that the broadly defined categories of early and late stage are heuristically useful (Kapczinski et al., 2014). Given the finding that response to an antidepressant correlates positively with gray matter volume of the anterior cingulate, insula, and right temporoparietal cortex (Chen et al., 2007), it is conceivable that antidepressants are basically efficacious in early stages of bipolar

disorder. Moreover, there is preliminary evidence of an increase in gray matter volume as a longitudinal effect of a lithium treatment (Moore et al., 2009). In the presence of structural brain alterations, neuroprotective drugs, such as lithium and valproic acid, might be the best treatment options since they may positively interact with neurotrophic processes potentially underlying the clinical symptoms (Chiu et al., 2013). This hypothesis can be tested by treatment studies using structural imaging at the onset and end of controlled treatments.

Abnormalities in the sense of *white matter hyperintensities* are often observed in older patients after cerebrovascular insults as well as in patients with migraine. In bipolar disorders, such alterations typically emerge at an early age before or shortly after the onset of the disorder (Hasler et al., 2006). This indicates that impairments of neuroplasticity and cellular resilience, which potentially lead to neural atrophy and cell death, are important pathological processes in bipolar disorder (Fries et al., 2014; Machado-Vieira et al., 2014). In accordance with this hypothesis is the observation that *white matter hyperintensities* predict a good response to treatment with lithium (Kato et al., 2000).

Magnetic resonance spectroscopy

MRS is a relatively new imaging method, which enables the measurement of the concentration of specific molecules. The most consistent MRS finding in bipolar disorder has been an increase in Glx in the prefrontal cortex (Gigante et al., 2012), namely in all examined prefrontal brain regions irrespective of medication. Glx reflects the total concentration of glutamate and glutamine. By interpreting this finding, one has to take into account that Glx is not a direct measurement of glutamatergic neurotransmission, because only 20% of glutamate in the brain serves as a neurotransmitter; 80% has a metabolic function. In this sense, bipolar disorder can be considered as a metabolic brain disorder. That blockade of mitochondrial metabolism leads to an increase of glutamate (Clausen et al., 2001) suggests that mitochondrial dysfunction plays a role in the pathogenesis of bipolar disorder (Stork and Renshaw, 2005). Mood stabilizing medications, such as

lithium, valproic acid, and lamotrigine, modulate the glutamate system; it would be important to know, in the sense of stratified medicine, whether or not there is a correlation between abnormal prefrontal Glx and efficacy of these medications. There is preliminary evidence for an association between low pretreatment glutamine levels and a good antidepressant efficacy of ketamine (Salvadore et al., 2012). As decreased Glx is relatively consistent, as per MRS findings in unipolar depression, Glx has the additional potential to enable a biologically valid differentiation between unipolar and bipolar affective disorders (Hasler and Northoff, 2011).

Immunology

Compared with the general population and with humans with unipolar depression, bipolar patients' risk of premature death is 1.5 to 3-fold increased, irrespective of the risk of suicide. The main reason for this excess mortality is thought to be the high comorbidity with somatic diseases: up to 80% of bipolar patients also suffer from metabolic and/or cardiovascular disease (Swartz and Fagiolini, 2012; Taylor and MacQueen, 2006). This high rate of somatic comorbidity cannot be explained only by unwanted side effects of pharmacotherapy or by unhealthy lifestyle; rather, it points to common pathogenetic processes. Based on immunological studies, it has been proposed that bipolar disorder be understood as a multisystem inflammatory disease (Leboyer et al., 2012). This hypothesis is based on the frequent observation of increased pro-inflammatory proteins, such as interleukin-6 and tumor necrosis factor alpha in both bipolar disorder and cardiovascular disease (Kunz et al., 2011). Interleukin-6 has appeared to be associated with illness progression and late stages of the disease (Grande et al., 2014). Therapies that act upon these immunologic processes will contribute to more targeted treatment in inflammation-associated bipolar disorders. Such treatments likely contribute to the reduction of excess morbidity and mortality in patients with bipolar disorder.

Stratified psychotherapy of bipolar disorders

Apart from psychoeducation, many forms of psychotherapy in bipolar disorders have proven effective. Interpersonal and social rhythm therapy, cognitive behavioral therapy, and family-focused therapy increase the probability of recovery, decrease time to recovery, and improve interpersonal skills and life satisfaction (Miklowitz, 2006). Similarly, pharmacotherapy response rates are typically low to moderate and scientific criteria on the selection of specific types of psychotherapy related to individual characteristics and the state of the illness are still lacking (Reinares et al., 2014). This lack can lead to long trial-and-error phases and may considerably reduce the effectiveness of psychological treatments. Psychotherapy research has labeled the lack of significant differences among effect sizes of available psychotherapies as the “Dodo bird verdict,” referring to Carroll’s novel “Alice’s Adventures in Wonderland,” in which Dodo said: “Everybody has won, and all must have prizes.” However, this verdict is only correct at the group level and there is evidence that responses to distinct therapeutic methods and distinct therapists vary considerably across individual patients. Staging and illness awareness may be particularly relevant predictors of the response to psychosocial interventions. For example, patients with no insight and willingness to participate in such interventions may particularly benefit from family psychoeducation, rather than from patient-focused interventions.

There are some promising leads that personality characteristics can predict responses to psychotherapy. For example, dependent personality traits may be a positive predictor of the response to highly structured behavioral therapy (Grawe, 2004). The state of an illness may be another important predictor of psychotherapy response. Data from controlled studies point to the finding that patients with only a few episodes benefit more from psychoeducation and psychotherapy than patients in late illness states (Reinares et al., 2014). In contrast, patients with chronic bipolar disorder may particularly benefit from psychological interventions that focus on specific functional impairments, such cognitive, interpersonal, and work-related deficits (Popovic et al., 2012; Torrent et al., 2013). Recent data suggest that functional remediation is not only effective in late stages of bipolar-I-disorder, but also of bipolar-II-disorder (Sole et al., 2014).

Many psychotherapies include a “personalization” of their interventions. For example, in behavioral activation, positive activities with antidepressant effects are systematically assessed, sometimes using extensive lists of potentially pleasurable activities. This kind of personalization of psychotherapies has great potential because it takes advantage of the fact that the response to behavioral change can usually be assessed easier and faster than the response to biological interventions. This potential should be used more systematically in the sense of stratified medicine.

The interpersonal and social rhythm therapy has been invented with the intention of specifically acting upon a disturbance of the circadian rhythm (Frank et al., 2005; Frank et al., 2000). This disturbance is likely an important process of disease in bipolar patients. An indication for it is the occurrence of hypomanic symptoms after sleep deprivation (Hasler et al., 2006). The relatively well-established biology and genetics of circadian rhythm will possibly contribute to the development of biomarkers that predict the response to treatments modifying the circadian rhythm.

Adverse drug reactions

Frequent problems with compliance and common somatic comorbidities in bipolar disorders means that drugs are not only chosen based on their effect but also based on their profile of adverse drug reactions (ADR). Stratification based on ADR profiles is relatively well advanced. The corrected QT interval derived from modern electrocardiogram machines is increasingly used to assess the threat of severe cardiac ADRs. This is particularly of great importance when drugs are combined since a drug-prolonging QTc can potentiate in drug combination. Risk factors of the metabolic syndrome—such as abdominal fat distribution and increased serum triglyceride, HDL cholesterol, blood pressure, and fasting glucose—represent relative contraindications for atypical antipsychotics, which cause frequent metabolic ADRs. Polysomnography can help to assess the danger of respiratory depressive psychotropic drugs. The identification of subjects carrying the HLA-B*1502 allele and the avoidance of carbamazepine therapy in these subjects has been strongly associated with a decrease in the incidence of carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis (Chen et al., 2011). The success of this “stratification” is considerable; despite increasing polypharmacy, the frequency of dangerous ADRs is decreasing (Greil et al., 2012).

Genetics

Genetic factors constitute approximately 90% of bipolar I disorder causes (Kieseppa et al., 2004; McGuffin et al., 2003). However, identification of individual risk genes is still unsuccessful. This is striking since risk genes have been found for complex genetic diseases with lower heritability than bipolar disorder, such as diabetes mellitus, Alzheimer’s disease, and breast cancer (Hasler et al., 2006).

As mentioned above, a major problem of psychiatric genetics is the fact that psychiatric disorders are defined as syndromal rather than based on pathologic processes. In this case, diverse pathological processes leading to the clinical image of bipolar disorder identification of risk genes of bipolar disorder as a symptom-based, defined phenotype is complicated or impossible (Kendler, 2006).

Another problem is the assessment of genetic variance. Even genome-wide association studies assess only a section of a possible variance; namely, the commonly occurring *single nucleotide polymorphisms* (SNPs). If, for example, very rare or spontaneous polymorphisms play an important role in the pathogenesis of bipolar disorders, they would not be detected by current methods (Kerner, 2014).

Recent new mathematical methods enable the computation of the amount of risk of illness contingent on SNPs, which are usually determined by GWAS studies (Kendler, 2013). A corresponding study showed that a 41% risk for bipolar I disorder is defined by the GWAS data of *Wellcome Trust Case Control Consortium* (Lee et al., 2011). This is considerably more than in schizophrenia (14–24%) or somatic diseases, such as Crohn's disease (24%) and diabetes mellitus type 1 (31%). This suggests that there is no fundamental hurdle regarding the way to the itemization of the genetics of bipolar disorders. Presumably, many genetic factors contribute to the risk of disease, each with a small effect. Such effects can be proven only in very large samples.

In bipolar disorders, the risk gene candidates with the best evidence are *CACNA1C* and *ANKK1* (Craddock and Sklar, 2013; Muhleisen et al., 2014). Both genes code for proteins regulate, as part of the ion channels, the neuronal excitability. These findings suggest that ion channels are decisive in the pathogenesis of bipolar disorders and drugs that act on ion channels may have therapeutic effects.

Regarding stratification of currently available therapies, genetic markers are crucial to predict treatment success. Thus far, identification of such markers has not been successful (Chen et al., 2014; Hou et al., 2014). GWAS studies exist at present exclusively for the effectiveness of lithium, which is in large part heritable according to family studies (Ewald et al., 1999; Turecki et al., 2001). These studies did not provide conclusive results, although they provided evidence that *GRIA2*, a protein of the AMPA glutamate receptor, plays a role in the lithium effect (Perlis et al., 2009). Genes related to

impulsivity and suicide risk such as IMPA1 and 2, INPP1, GSK3 α and β (Jimenez et al., 2013) may also be candidate genetic markers for the response to lithium.

Candidate gene studies also showed that the gene *XBP1*, which affects cellular reactions to stress, may be a potential predictor of the therapeutic effect of valproic acid (Kim et al., 2009). Candidate genes for the prediction of the effect of lithium in bipolar patients, including the BDNF Met allele of rs6265 coding for an important neurotrophic factor, plays an important role in brain aging processes and chronification of psychiatric disorders (Salehi et al., 2013; Wang et al., 2012). Studies on the effect of monoaminergic antidepressants show that polymorphisms of the serotonin transporter gene and the gene for serotonin receptor 5HT1A have the potential to assess the antidepressant effect (Serretti et al., 2004; Severino et al., 2013; Zanardi et al., 2001).

Epigenetics

Each cell of our body contains an epigenetic imprint of experience in its genome. Some epigenetic changes can be inherited through multiple generations. The epigenetic patterning occurs at the level of whole chromosomes and of large chromosomal regions down to the single nucleotide level. A relatively well-examined epigenetic change involves the acetylation of histones leading to the local loosening of DNA and increased gene reading in this section. In contrast, histone methylation inhibits gene expression in specific gene sections. At the level of the DNA, methylation and demethylation of DNA inhibit and, respectively, enhance the expression of specific genes (Pena et al., 2014).

There is preliminary evidence for epigenetic changes playing a role in the pathogenesis of bipolar disorders (Xiao et al., 2014). Preliminary findings suggest that the cerebral epigenetic inhibition of the GABAergic gene expression contribute to the development of bipolar disorders (Guidotti et al., 2011). A typical trait of this pathology is a low expression of glutamic acid decarboxylase 67 (GAD67), which synthesizes GABA. This results in attenuation of the inhibiting GABA system.

Pathogenic DNA sequences are very stable whereas epigenetic changes are reversible and therefore qualify for pharmacological targets. Valproic acid is a potent inhibitor of various histone deacetylases (HDACs). It has been showed that valproic acid specifically encourages the promoter demethylation of the *GAD67* gene and, therefore, *GAD67* expression (Dong et al., 2010). Other drugs promoting DNA methylation applied in bipolar disorders are clozapine and sulpiride (Dong et al., 2008).

All of these findings suggest that epigenetic changes have a great potential to improve the stratification of psychiatric treatment as biomarkers. Yet the main problem is that the majority of epigenetic changes are specific for cells and tissues. To what extent epigenetic changes measured in blood cells provide information about the epigenome of the brain is currently unclear.

Conclusion

The current process of diagnosing bipolar disorders based solely on clinical symptoms has crucial weaknesses. Evidence for these weaknesses are low average response rates, long phases of treatment adjustment, and inconsistent treatment guidelines.

Employing methods of neuropsychology, neuroradiology, immunology, genetics, and epigenetics, biomarkers have been proposed and evaluated. Table 2 summarizes the most promising clinical and biological markers to predict responses to specific treatments. To date, the most reliable markers are derived from psychopathology and history taking. Although there are a number of promising leads, no neuropsychological or biological markers have been found thus far that reliably predict individual therapy effectiveness.

NIMH's Research Domain Criteria (RDoC) (Morris and Cuthbert, 2012) provides a promising new research framework that takes a dimensional approach to the study of the genetic, neural and behavioral features of mental disorders. The domains "negative valence system" related to stress sensitivity and anxiety, "positive valence system" related to reward processing, and "systems for

social processes” may be particularly important for the study of bipolar disorders. The main limitation of such a neuroscience-based approach to psychiatric diagnostics has been the missing link between clinical states and biomarkers (Fava et al., 2014). A transition from DSM to RDoC will have to incorporate various combinations DSM disorder categories and dimensional RDOC constructs in experiments (Cuthbert, 2014) . However, the high clinical utility of DSM concepts will likely be a major obstacle in this transition. In addition, the RDoC approach emphasizes cross-sectional assessment, while abnormal neurodevelopment is an important aspect in the pathogenesis of bipolar disorder. Identifying sensitive periods for the RDoC constructs will improve understanding of environmental pathogenetic components and enhance the precision of stage-related therapeutic interventions (Casey et al., 2014). Changing the paradigm for drug development for bipolar disorders based on the RDoC proposal may counteract the declining assay sensitivity of clinical trials and contribute to moving clinical research toward hard outcomes, such as biomarkers, and ecological measures of functional benefits (Vieta, 2014).

For clinicians, it is important to completely exploit clinical markers predicting therapy effects in bipolar disorders, including degree of severity, type I/II classification, typical course of illness, family anamnesis, mixed states of manic and depressive phases, predominant polarity, degree of agitation, and suicidal risk (Fava et al., 2014).

The best current predictors for treatment success are previous responses to a certain treatment and the evidence of an effective treatment in relatives with bipolar disorder.

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Table 1. Predictors of bipolar spectrum disorders

Predictor
<ul style="list-style-type: none">• Early onset of disease• Large number of depressive episodes• Bipolar disorders in the family history• Occurrence of individual maniform symptoms• Atypical depressive symptoms• Cyclothymic temperament

Table 2. Clinical and biomarkers related to treatment response in bipolar disorders

State specifier	Favorable response to	References
Mixed episode	Olanzapine, asenapine	(Grunze and Azorin, 2014; Kruger et al., 2005) (Brown et al., 2013; Gonzalez et al., 2013; Kwentus et al., 2012; McIntyre et al., 2009) (Geddes and Miklowitz, 2013) (Kohler et al., 2014) (Baldessarini et al., 2006)
Agitation in manic episodes	Asenapine, loxapine, aripiprazole	
Severe depressive episodes	Combination treatments	
Mild depressive episodes	Psychotherapy	
High suicidal risk	Lithium	
Course specifier		
Predominantly manic	Quetiapine, lithium, olanzapine, ziprasidone, aripiprazole, risperidone, caregiver group psychoeducation	(Popovic et al., 2012; Popovic et al., 2013) (Popovic et al., 2012; Popovic et al., 2013) (Geddes and Miklowitz, 2013) (Golden et al., 2005)
Predominantly depressive	Lamotrigine, psychotherapy	
Typical manic-depressive course with full interepisode remission	Lithium	
Seasonal affective disorder (SAD)	Light therapy	
Neuropsychological specifier		
Dependent personality traits	Highly structured behavioral therapy	(Grawe, 2004) (Geddes and Miklowitz, 2013; Reinares et al., 2014) (Geddes and Miklowitz, 2013; Reinares et al., 2014)
High cognitive functioning	Cognitive behavioral therapy (CBT)	
Low cognitive functioning	Functional remediation	

Stage of illness		
Early states	Psychotherapy, psychoeducation, medication	(Reinares et al., 2014)
Late states	Cognitive and functional remediation, social work	(Reinares et al., 2014)
Imaging biomarkers		
Hyperactivity in limbic brain regions	Antidepressants, deep brain stimulation	(Chen et al., 2007;
Low activity in limbic brain regions	Thyroid hormones (uncertain)	Mayberg et al., 1997;
White matter hyperintensity	Lithium	Mayberg et al., 2005)
Gray matter volume reductions	Lithium	(Kato et al., 2000)
		(Chiu et al., 2013; Moore et al., 2009)
Genetic markers		
XBP1, G allele of rs2269577	Valproic acid	(Kim et al., 2009)
BDNF, Met allele of rs6265	Lithium	(Wang et al., 2012)
5-HTTLR, I allele	SSRI co-medication	(Zanardi et al., 2001)
HTR1A, CC genotype of rs6295	Fluvoxamine co-medication	(Serretti et al., 2004)